

(19) World Intellectual Property Organization
International Bureau



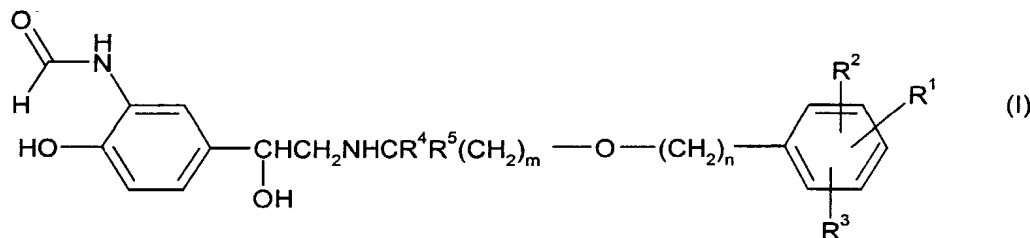
(43) International Publication Date
3 October 2002 (03.10.2002)

PCT

(10) International Publication Number
WO 02/076933 A1

- (51) International Patent Classification⁷: **C07C 311/29**, A61K 31/18, A61P 11/06, 29/00
- (21) International Application Number: PCT/EP02/03122
- (22) International Filing Date: 20 March 2002 (20.03.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
0107213.1 22 March 2001 (22.03.2001) GB
0126995.0 9 November 2001 (09.11.2001) GB
- (71) Applicant (for all designated States except US): **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **BIGGADIKE, Keith** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage SG1 2NY (GB). **FIELD, Rita** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage SG1 2NY (GB). **GUNTRIP, Stephen, Barry** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage SG1 2NY (GB). **LOOKER BRIAN, Edgar** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage SG1 2NY (GB).
- (74) Agent: **FLORENCE, Julia, Anne**; Corporate Intellectual Property, GlaxoSmithKline, 980 Great West Road (CN925.1), Brentford, Middlesex TW8 9GS (GB).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: FORMYLIDE DERIVATIVES AS BETA2-ADRENORECEPTOR AGONISTS



(57) Abstract: The present invention relates to novel compounds of formula (I), to a process for their manufacture, to pharmaceutical compositions containing them, and to their use in therapy, in particular their use in the prophylaxis and treatment of respiratory diseases.

FORMANILIDE DERIVATIVES AS BETA2-ADRENORECEPTOR AGONISTS

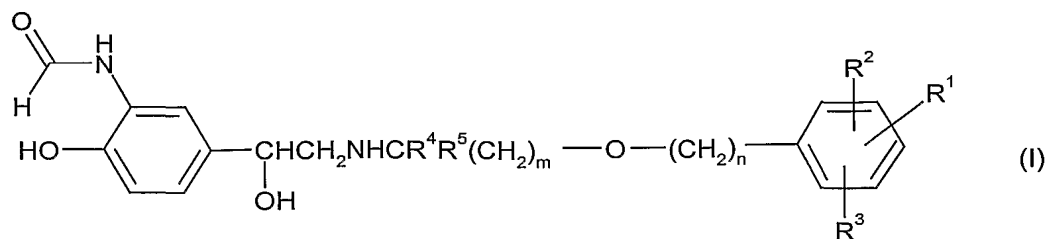
The present invention is concerned with phenethanolamine derivatives, processes for their preparation, compositions containing them and their use in medicine, particularly in the prophylaxis and treatment of respiratory diseases.

Certain phenethanolamine compounds are known in the art as having selective stimulant action at β_2 -adrenoreceptors and therefore having utility in the treatment of bronchial asthma and related disorders. Thus GB 2 140 800 describes phenethanolamine compounds including 4-hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol 1-hydroxy-2-naphthalenecarboxylate (salmeterol xinafoate) which is now used clinically in the treatment of such medical conditions.

Formoterol, i.e. 2'-hydroxy-5'-[(RS)-1-hydroxy-2{[(RS)-p-methoxy- α -methylphenethyl]amino}ethyl]formanilide (US 3994974), particularly its fumarate salt is another well-known adrenoreceptor agonist which is now used clinically in the treatment of bronchial asthma and related disorders.

Although salmeterol and the other commercially available β_2 -adrenoreceptor agonists are effective bronchodilators, the maximum duration of action is 12 hours, hence twice daily dosing is often required. There is therefore a clinical need for compounds having potent and selective stimulant action at β_2 -adrenoreceptors and having an advantageous profile of action.

According to the present invention, there is provided a compound of formula (I)



or a salt, solvate, or physiologically functional derivative thereof, wherein:

m is an integer of from 2 to 8;

5 n is an integer of from 3 to 11, preferably from 3 to 7;

with the proviso that m + n is 5 to 19, preferably 5 to 12;

R^1 is $-XSO_2NR^6R^7$

10 wherein X is $-(CH_2)_p-$ or C_{2-6} alkenylene;

R^6 and R^7 are independently selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, $C(O)NR^8R^9$, phenyl, and phenyl (C_{1-4} alkyl)-, or R^6 and R^7 , together with the nitrogen to which they are bonded, form a 5-, 6-, or 7-membered nitrogen containing ring,

15 and R^6 and R^7 are each optionally substituted by one or two groups selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, hydroxy-substituted C_{1-6} alkoxy, $-CO_2R^8$, $-SO_2NR^8R^9$, $-CONR^8R^9$, $-NR^8C(O)R^9$, or a 5-, 6- or 7-membered heterocyclic ring;

R^8 and R^9 are independently selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, and phenyl (C_{1-4} alkyl)-; and

20 p is an integer of from 0 to 6, preferably from 0 to 4;

R^2 and R^3 are independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, halo, phenyl, and C_{1-6} haloalkyl;

25 R^4 and R^5 are independently selected from hydrogen and C_{1-4} alkyl with the proviso that the total number of carbon atoms in R^4 and R^5 is not more than 4.

In the compounds of formulae (I) and R^1 is preferably $-SO_2NR^6R^7$ wherein R^6 and R^7 are independently selected from hydrogen and C_{1-6} alkyl, more preferably R^1 is

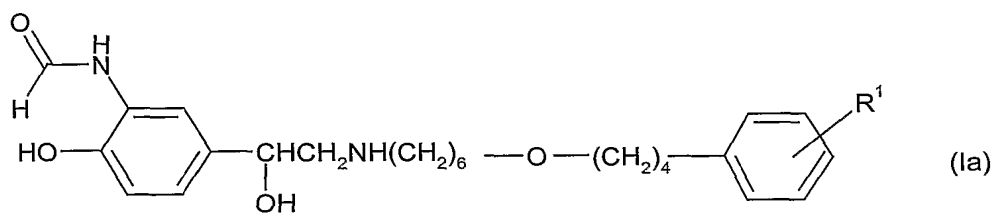
30 $-SO_2NH_2$.

In the compounds of formula (I) the group R^1 is preferably attached to the meta-position relative to the $-O-(CH_2)_n-$, $-O-(CH_2)_4-$ or $-O-(CH_2)_3-$ link respectively.

In the compounds of formula (I), R^4 and R^5 are preferably independently selected from hydrogen and methyl, more preferably R^4 and R^5 are both hydrogen.

- 5 In the compounds of formula (I), m is suitably 4, 5, or 6, and preferably m is 5, and n is suitably 3, 4, 5 or 6. Preferably m is 5 or 6 and n is 3 or 4 such that m + n is 8, 9 or 10, preferably 9.

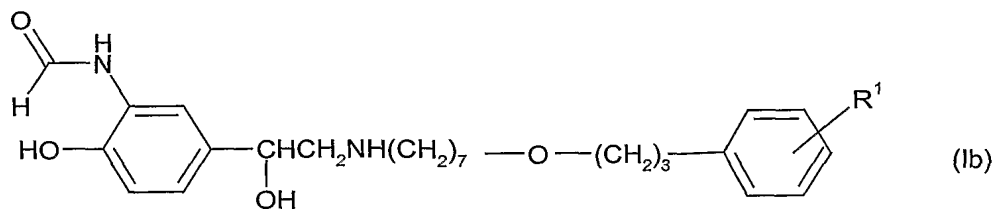
- 10 According to a preferred aspect of the invention, there is provided a compound of formula (Ia)



- 15 or a salt, solvate, or physiologically functional derivative thereof, wherein

R^1 is as defined above for formula (I).

- 20 According to a further preferred aspect of the invention, there is provided a compound of formula (Ib)



- 25 or a salt, solvate, or physiologically functional derivative thereof, wherein
- R^1 is as defined above for formula (I).

In the compounds of formulae (Ia) and (Ib), R¹ is preferably -SO₂NR⁶R⁷ wherein R⁶ and R⁷ are independently selected from hydrogen and C₁₋₆alkyl, more preferably R¹ is -SO₂NH₂.

In the compounds of formulae (Ia) and (Ib), the group R¹ is preferably attached to the meta-position relative to the -O-(CH₂)_n-, -O-(CH₂)₄- or -O-(CH₂)₃- link respectively.

It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove.

Preferred compounds of the invention include:

3-(4-{{6-({2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl[oxy]butyl)benzenesulfonamide; and
N-(tert-butyl)-3-(4-{{6-({2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl[oxy]butyl)benzenesulfonamide;

and salts, solvates, and physiologically functional derivatives thereof.

In the definition of R¹, the term "5-, 6-, or 7- membered nitrogen containing ring" means a 5-, 6-, or 7- membered saturated or unsaturated ring which includes a nitrogen atom and optionally 1 or 2 other heteroatoms independently selected from nitrogen, sulphur, and oxygen. Suitable examples of such a ring include piperidinyl, morpholinyl, and piperazinyl.

In the definition of R¹, the term "5-, 6-, or 7- membered heterocyclic ring" means a 5-, 6-, or 7- membered saturated or unsaturated ring which includes 1, 2 or 3 heteroatoms independently selected from nitrogen, sulphur, and oxygen. Suitable examples of such a ring include piperidinyl, morpholinyl, and piperazinyl.

In the definition of X, the term "alkenylene" includes both *cis* and *trans* structures. Suitable examples of alkenylene groups include -CH=CH-.

The compounds of formulae (I), (Ia) and (Ib) include an asymmetric centre, namely the carbon atom of the



group. The present invention includes both (S) and (R) enantiomers either in substantially pure form or admixed in any proportions.

Similarly, where R⁴ and R⁵ are different groups, the carbon atom to which they are attached is an asymmetric centre and the present invention includes both (S) and (R) enantiomers at this centre either in substantially pure form or admixed in any proportions.

Thus the compounds of formulae (I), (Ia) and (Ib) include all enantiomers and diastereoisomers as well as mixtures thereof in any proportions.

Particularly preferred compounds of the invention include:

3-(4-{{6-({(2R)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl}oxy}butyl)benzenesulfonamide;

3-(4-{{6-({(2S)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl}oxy}butyl)benzenesulfonamide;

3-(4-{{6-({(2R/S)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl}oxy}butyl)benzenesulfonamide;

N-(tert-butyl)-3-(4-{{6-({(2R)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl}oxy}butyl)benzenesulfonamide;

N-(tert-butyl)-3-(4-{{6-({(2S)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl}oxy}butyl)benzenesulfonamide;

N-(tert-butyl)-3-(4-{{6-({(2R/S)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl}oxy}butyl)benzenesulfonamide;

and salts, solvates, and physiologically functional derivatives thereof.

Salts and solvates of compounds of formulae (I), (Ia) and (Ib) which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically

acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formulae (I), (Ia) and (Ib) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives.

By the term "physiologically functional derivative" is meant a chemical derivative of a compound of formula (I), (Ia) or (Ib) having the same physiological function as the free compound of formula (I), (Ia) or (Ib), for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

Suitable salts according to the invention include those formed with both organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, sulphamic, sulphanilic, succinic, oxalic, fumaric, maleic, malic, glutamic, aspartic, oxaloacetic, methanesulphonic, ethanesulphonic, arylsulphonic (for example p-toluenesulphonic, benzenesulphonic, naphthalenesulphonic or naphthalenedisulphonic), salicylic, glutaric, gluconic, tricarballic, cinnamic, substituted cinnamic (for example, methyl, methoxy or halo substituted cinnamic, including 4-methyl and 4-methoxycinnamic acid), ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), naphthaleneacrylic (for example naphthalene-2-acrylic), benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, benzenecrylic (for example 1,4-benzenediacrylic) and isethionic acids. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexyl amine and N-methyl-D-glucamine.

Pharmaceutically acceptable esters of the compounds of formulae (I), (Ia) and (Ib) may have a hydroxyl group converted to a C₁₋₆alkyl, aryl, aryl C₁₋₆ alkyl, or amino acid ester.

As mentioned above, the compounds of formulae (I), (Ia) and (Ib) are selective β_2 -adrenoreceptor agonists as demonstrated using functional or reporter gene readout from cell lines transfected with human beta-adrenoreceptors as described below.

Compounds according to the present invention also have the potential to combine long duration of effect with rapid onset of action. Furthermore, certain compounds have shown an improved therapeutic index in animal models relative to existing long-acting β_2 -agonist bronchodilators. As such, compounds of the invention may be suitable for once-daily administration.

Therefore, compounds of formulae (I), (Ia) and (Ib) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have use in the prophylaxis and treatment of clinical conditions for which a selective β_2 -adrenoreceptor agonist is indicated. Such conditions include diseases associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease (e.g. rhinitis, including seasonal and allergic rhinitis).

Other conditions which may be treated include premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

Accordingly, the present invention provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. In particular, the present invention provides such a method for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect the present invention provides such a method for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic,

and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle wasting disease.

In the alternative, there is also provided a compound of formula (I), (Ia) or (Ib) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy, particularly, for use in the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist is indicated. In particular, there is provided a compound of formula (I), (Ia) or (Ib) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect, there is provided a compound of formula (I), (Ia) or (Ib) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle wasting disease.

The present invention also provides the use of a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2 -adrenoreceptor agonist is indicated, for example a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect, there is provided a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

The amount of a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. The compounds of the invention may be administered by inhalation at a dose of from 0.0005mg to 10 mg, preferably 0.005mg to 0.5mg. The dose range for adult humans is generally from 0.0005 mg to 100mg per day and preferably 0.01 mg to 1mg per day.

While it is possible for the compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to be administered alone, it is preferable to present it as a pharmaceutical formulation.

Accordingly, the present invention further provides a pharmaceutical formulation comprising a compound of formula (I), (Ia) or (Ib) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

Hereinafter, the term "active ingredient" means a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), intranasal, inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with

liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Formulations

generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier substance) such as lactose or starch. Use of lactose is preferred. Each capsule or cartridge may generally contain between 20 μ g-10mg of the compound of formula (I) optionally in combination with another therapeutically active ingredient. Alternatively, the compound of the invention may be presented without excipients. Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered (eg as in Diskus, see GB 2242134 or Diskhaler, see GB 2178965, 2129691 and 2169265) or metered in use (eg as in Turbuhaler, see EP 69715). An example of a unit-dose device is Rotahaler (see GB 2064336). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a compound of formula (I) preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

Spray compositions for topical delivery to the lung by inhalation may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the compound of formula (I) optionally in combination with another therapeutically active ingredient and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant. The aerosol composition may be excipient free or may optionally contain additional formulation excipients well known in the art such as surfactants eg oleic acid

or lecithin and cosolvents eg ethanol. Pressurised formulations will generally be retained in a canister (eg an aluminium canister) closed with a valve (eg a metering valve) and fitted into an actuator provided with a mouthpiece.

- 5 Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10 μ m, preferably 2-5 μ m. Particles having a size above 20 μ m are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient as produced may be size reduced by conventional means eg by
- 10 micronisation. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline. When an excipient such as lactose is employed, generally, the particle size of the excipient will be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as milled lactose, wherein not more than 85% of lactose particles
- 15 will have a MMD of 60-90 μ m and not less than 15% will have a MMD of less than 15 μ m.

- Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or
- 20 presented as a non-sterile product.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

- 25 Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.
- 30 Preferred unit dosage formulations are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

5

The compounds and pharmaceutical formulations according to the invention may be used in combination with or include one or more other therapeutic agents, for example anti-inflammatory agents, anticholinergic agents (particularly an M_1 , M_2 , M_1/M_2 or M_3 receptor antagonist), other β_2 -adrenoreceptor agonists, antiinfective agents (e.g. antibiotics, antivirals), or antihistamines. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with one or more other therapeutically active agents, for example, an anti-inflammatory agent (for example a corticosteroid or an NSAID), an anticholinergic agent, another β_2 -adrenoreceptor agonist, an antiinfective agent (e.g. an antibiotic or an antiviral), or an antihistamine. Preferred are combinations comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid, and/or an anticholinergic, and/or a PDE-4 inhibitor. Preferred combinations are those comprising one or two other therapeutic agents.

20

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, (e.g. as alkali metal or amine salts or as acid addition salts), or prodrugs, or as esters (e.g. lower alkyl esters), or as solvates (e.g. hydrates) to optimise the activity and/or stability and/or physical characteristics (e.g. solubility) of the therapeutic ingredient. It will be clear also that where appropriate, the therapeutic ingredients may be used in optically pure form.

25

Suitable anti-inflammatory agents include corticosteroids and NSAIDs. Suitable corticosteroids which may be used in combination with the compounds of the invention are those oral and inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity. Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, $6\alpha,9\alpha$ -difluoro- 17α -[(2-furanylcabonyl)oxy]- 11β -hydroxy- 16α -methyl-3-oxo-androsta-1,4-diene- 17β -carbothioic acid S-fluoromethyl

30

ester, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxy- androsta-1,4-diene-17 β -carbothioic acid S-(2-oxo-tetrahydro-furan-3S-yl) ester, beclomethasone esters (e.g. the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone acetonide, rofleponide, ciclesonide, butixocort propionate, RPR-106541, and ST-126. Preferred corticosteroids include fluticasone propionate, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester and 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester, more preferably 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester.

Suitable NSAIDs include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (e.g. chemokine antagonists) or inhibitors of cytokine synthesis. Suitable other β_2 -adrenoreceptor agonists include salmeterol (e.g. as the xinafoate), salbutamol (e.g. as the sulphate or the free base), formoterol (e.g. as the fumarate), fenoterol or terbutaline and salts thereof.

Of particular interest is use of the compound of formula (I) in combination with a phosphodiesterase 4 (PDE4) inhibitor or a mixed PDE3/PDE4 inhibitor. The PDE4-specific inhibitor useful in this aspect of the invention may be any compound that is known to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not compounds which inhibit other members of the PDE family as well as PDE4. Generally it is preferred to use a PDE4 inhibitor which has an IC₅₀ ratio of about 0.1 or greater as regards the IC₅₀ for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC₅₀ for the form which binds rolipram with a low affinity. For the purposes of this disclosure, the cAMP catalytic site which binds R and S rolipram with a low affinity is denominated the "low affinity" binding site (LPDE 4) and the other form of this catalytic site which binds rolipram with a high

affinity is denominated the "high affinity" binding site (HPDE 4). This term "HPDE4" should not be confused with the term "hPDE4" which is used to denote human PDE4. Initial experiments were conducted to establish and validate a [³H]-rolipram binding assay. Details of this work are given in the Binding Assays described in detail below.

5

The preferred PDE4 inhibitors of use in this invention will be those compounds which have a salutary therapeutic ratio, i.e., compounds which preferentially inhibit cAMP catalytic activity where the enzyme is in the form that binds rolipram with a low affinity, thereby reducing the side effects which apparently are linked to inhibiting the form which binds rolipram with a high affinity. Another way to state this is that the preferred compounds will have an IC₅₀ ratio of about 0.1 or greater as regards the IC₅₀ for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC₅₀ for the form which binds rolipram with a low affinity.

10

15

A further refinement of this standard is that of one wherein the PDE4 inhibitor has an IC₅₀ ratio of about 0.1 or greater; said ratio is the ratio of the IC₅₀ value for competing with the binding of 1nM of [³H]R-rolipram to a form of PDE4 which binds rolipram with a high affinity over the IC₅₀ value for inhibiting the PDE4 catalytic activity of a form which binds rolipram with a low affinity using 1 μM[³H]-cAMP as the substrate.

20

Examples of useful PDE4 inhibitors are:

(R)-(+)-1-(4-bromobenzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone;
(R)-(+)-1-(4-bromobenzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone;
3-(cyclopentyloxy-4-methoxyphenyl)-1-(4-N'-[N2-cyano-S-methyl-isothioureido]benzyl)-
2-pyrrolidone;
cis 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid];
cis-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol];
(R)-(+)-ethyl [4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidine-2-ylidene]acetate; and
(S)-(-)-ethyl [4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidine-2-ylidene]acetate.

25

30

Most preferred are those PDE4 inhibitors which have an IC₅₀ ratio of greater than 0.5, and particularly those compounds having a ratio of greater than 1.0. Preferred compounds are *cis* 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-

carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]; these are examples of compounds which bind preferentially to the low affinity binding site and which have an IC₅₀ ratio of 0.1 or greater.

Other compounds of interest include:

Compounds set out in U.S. patent 5,552,438 issued 03 September, 1996; this patent and the compounds it discloses are incorporated herein in full by reference. The compound of particular interest, which is disclosed in U.S. patent 5,552,438, is *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also known as cilomast) and its salts, esters, pro-drugs or physical forms;

AWD-12-281 from Asta Medica (Hofgen, N. *et al.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98; CAS reference No. 247584020-9); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa Hakko in WO99/16766; K-34 from Kyowa Hakko; V-11294A from Napp (Landells, L.J. *et al.* Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-23, Geneva) 1998] 1998, 12 (Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a pthalazinone (WO99/47505, the disclosure of which is hereby incorporated by reference) from Byk-Gulden; Pumafentrine, (-)-p-[(4aR*,10bS*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide which is a mixed PDE3/PDE4 inhibitor which has been prepared and published on by Byk-Gulden, now Altana; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from Vemalis; or T-440 (Tanabe Seiyaku; Fuji, K. *et al.* J Pharmacol Exp Ther, 1998, 284(1): 162), and T2585.

Other possible PDE-4 and mixed PDE3/PDE4 inhibitors include those listed in WO01/13953, the disclosure of which is hereby incorporated by reference.

Phosphodiesterase and Rolipram Binding Assays

Assay method 1A

Isolated human monocyte PDE4 and hrPDE (human recombinant PDE4) was determined to exist primarily in the low affinity form. Hence, the activity of test compounds against the low affinity form of PDE4 can be assessed using standard assays for PDE4 catalytic activity employing 1 μ M [3 H]cAMP as a substrate (Torphy et al., J. of Biol. Chem., Vol. 267, No. 3 pp1798-1804, 1992).

Rat brain high speed supernatants were used as a source of protein and both enantiomers of [3 H]-rolipram were prepared to a specific activity of 25.6 Ci/mmol. Standard assay conditions were modified from the published procedure to be identical to the PDE assay conditions, except for the last of the cAMP: 50mM Tris HCl (pH 7.5), 5 mM MgCl₂, 50 μ M 5'-AMP and 1 nM of [3 H]-rolipram (Torphy et al., J. of Biol. Chem., Vol. 267, No. 3 pp1798-1804, 1992). The assay was run for 1 hour at 30° C. The reaction was terminated and bound ligand was separated from free ligand using a Brandel cell harvester. Competition for the high affinity binding site was assessed under conditions that were identical to those used for measuring low affinity PDE activity, expect that [3 H]-cAMP was not present.

Assay method 1B

Measurement of Phosphodiesterase Activity

PDE activity was assayed using a [3 H]cAMP SPA or [3 H]cGMP SPA enzyme assay as described by the supplier (Amersham Life Sciences). The reactions were conducted in 96-well plates at room temperature, in 0.1 ml of reaction buffer containing (final concentrations): 50 mM Tris-HCl, pH 7.5, 8.3 mM MgCl₂, 1.7 mM EGTA, [3 H]cAMP or [3 H] cGMP (approximately 2000 dpm/pmol), enzyme and various concentrations of the inhibitors. The assay was allowed to proceed for 1 hr and was terminated by adding 50 μ l of SPA yttrium silicate beads in the presence of zinc sulfate. The plates were shaken and allowed to stand at room temperature for 20 min. Radiolabeled product formation was assessed by scintillation spectrometry.

[3 H]R-rolipram binding assay

The [3 H]R-rolipram binding assay was performed by modification of the method of Schneider and co-workers, see Nicholson, et al., Trends Pharmacol. Sci., Vol. 12, pp.19-27 (1991) and McHale et al., Mol. Pharmacol., Vol. 39, 109-113 (1991). R-Rolipram binds to the catalytic site of PDE4 see Torphy et al., Mol. Pharmacol., Vol. 39,

pp. 376-384 (1991). Consequently, competition for [³H]R-rolipram binding provides an independent confirmation of the PDE4 inhibitor potencies of unlabeled competitors. The assay was performed at 30°C for 1 hr in 0.5 µl buffer containing (final concentrations): 50 mM Tris-HCl, pH 7.5, 5 mM MgCl₂, 0.05% bovine serum albumin, 2 nM [³H]R-rolipram (5.7 x 10⁴ dpm/pmol) and various concentrations of non-radiolabeled inhibitors. The reaction was stopped by the addition of 2.5 ml of ice-cold reaction buffer (without [³H]-R-rolipram) and rapid vacuum filtration (Brandel Cell Harvester) through Whatman GF/B filters that had been soaked in 0.3% polyethylenimine. The filters were washed with an additional 7.5 ml of cold buffer, dried, and counted via liquid scintillation spectrometry.

Suitable anticholinergic agents are those compounds that act as antagonists at the muscarinic receptor, in particular those compounds which are antagonists of the M₁ and M₂ receptors. Exemplary compounds include the alkaloids of the belladonna plants as illustrated by the likes of atropine, scopolamine, homatropine, hyoscyamine; these compounds are normally administered as a salt, being tertiary amines. These drugs, particularly the salt forms, are readily available from a number of commercial sources or can be made or prepared from literature data via, to wit:

Atropine - CAS-51-55-8 or CAS-51-48-1 (anhydrous form), atropine sulfate - CAS-5908-99-6; atropine oxide - CAS-4438-22-6 or its HCl salt - CAS-4574-60-1 and methylatropine nitrate - CAS-52-88-0.

Homatropine - CAS-87-00-3, hydrobromide salt - CAS-51-56-9, methylbromide salt - CAS-80-49-9.

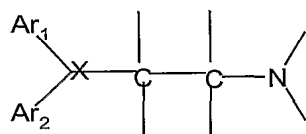
Hyoscyamine (*d, l*) - CAS-101-31-5, hydrobromide salt - CAS-306-03-6 and sulfate salt - CAS-6835-16-1.

Scopolamine - CAS-51-34-3, hydrobromide salt - CAS-6533-68-2, methylbromide salt - CAS-155-41-9.

Preferred anticholinergics include ipratropium (e.g. as the bromide), sold under the name Atrovent, oxitropium (e.g. as the bromide) and tiotropium (e.g. as the bromide) (CAS-139404-48-1). Also of interest are: methantheline (CAS-53-46-3), propantheline bromide (CAS- 50-34-9), anisotropine methyl bromide or Valpin 50 (CAS- 80-50-2), clidinium bromide (Quarzan, CAS-3485-62-9), copyrrolate (Robinul), isopropamide

iodide (CAS-71-81-8), mepenzolate bromide (U.S. patent 2,918,408), tridihexethyl chloride (Pathilone, CAS-4310-35-4), and hexocyclium methylsulfate (Tral, CAS-115-63-9). See also cyclopentolate hydrochloride (CAS-5870-29-1), tropicamide (CAS-1508-75-4), trihexyphenidyl hydrochloride (CAS-144-11-6), pirenzepine (CAS-29868-97-1), telenzepine (CAS-80880-90-9), AF-DX 116, or methoctramine, and the
 5 compounds disclosed in WO01/04118, the disclosure of which is hereby incorporated by reference.

Suitable antihistamines (also referred to as H₁-receptor antagonists) include any one or
 10 more of the numerous antagonists known which inhibit H₁-receptors, and are safe for human use. All are reversible, competitive inhibitors of the interaction of histamine with H₁-receptors. The majority of these inhibitors, mostly first generation antagonists, have a core structure, which can be represented by the following formula:



15

This generalized structure represents three types of antihistamines generally available: ethanolamines, ethylenediamines, and alkylamines. In addition, other first generation antihistamines include those which can be characterized as based on piperazine and
 20 phenothiazines. Second generation antagonists, which are non-sedating, have a similar structure-activity relationship in that they retain the core ethylene group (the alkylamines) or mimic the tertiary amine group with piperazine or piperidine. Exemplary antagonists are as follows:

Ethanolamines: carbinoxamine maleate, clemastine fumarate, diphenylhydramine
 25 hydrochloride, and dimenhydrinate.

Ethylenediamines: pyrillamine amleate, tripelennamine HCl, and tripelennamine citrate.

Alkylamines: chlorpheniramine and its salts such as the maleate salt, and acrivastine.

Piperazines: hydroxyzine HCl, hydroxyzine pamoate, cyclizine HCl, cyclizine lactate, meclizine HCl, and cetirizine HCl.

30 Piperidines: Astemizole, levocabastine HCl, loratadine or its descarboethoxy analogue, and terfenadine and fexofenadine hydrochloride or another pharmaceutically acceptable salt.

Azelastine hydrochloride is yet another H₁ receptor antagonist which may be used in combination with a PDE4 inhibitor.

Examples of preferred anti-histamines include methapyrilene and loratadine.

5 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor.

10 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid.

15 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic.

20 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an antihistamine.

25 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor and a corticosteroid.

30 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic and a PDE-4 inhibitor.

35 The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a physiologically acceptable diluent or carrier represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

5

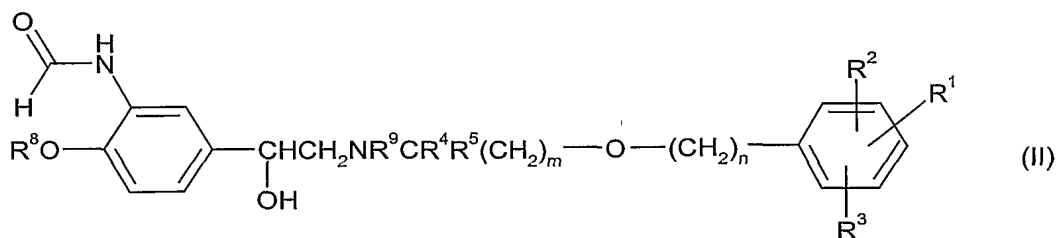
According to a further aspect of the invention, there is provided a process for preparing a compound of formula (I), (Ia) or (Ib) or a salt, solvate, or physiologically functional derivative thereof which comprises a process as defined below followed by the following steps in any order:

10

- (i) optional removal of any protecting groups;
- (ii) optional separation of an enantiomer from a mixture of enantiomers;
- (iii) optional conversion of the product to a corresponding salt, solvate, or physiologically functional derivative thereof.

15

In one general process, a compound of formula (I), (Ia) or (Ib) may be obtained by deprotection of a protected intermediate, for example of formula (II):



20

or a salt or solvate thereof, wherein R^1 , R^2 , R^3 , R^4 , R^5 , m , and n are as defined for the compound of formula (I), (Ia) or (Ib), and R^8 , and R^9 are each independently either hydrogen or a protecting group provided that at least one of R^8 , and R^9 is a protecting group.

25

Suitable protecting groups may be any conventional protecting group such as those described in "Protective Groups in Organic Synthesis" by Theodora W Greene and Peter G M Wuts, 3rd edition (John Wiley & Sons, 1999). Examples of suitable hydroxyl protecting groups represented by R^8 are esters such as acetate ester, aralkyl groups

such as benzyl, diphenylmethyl, or triphenylmethyl, and tetrahydropyranyl. Examples of suitable amino protecting groups represented by R⁹ include benzyl, α -methylbenzyl, diphenylmethyl, triphenylmethyl, benzyloxycarbonyl, tert-butoxycarbonyl, and acyl groups such as trichloroacetyl or trifluoroacetyl.

5

As will be appreciated by the person skilled in the art, use of such protecting groups may include orthogonal protection of groups in the compounds of formula (II) to facilitate the selective removal of one group in the presence of another, thus enabling selective functionalisation of a single amino or hydroxyl function. For example, the -CH(OH)

10 group may be orthogonally protected using, for example, a trialkylsilyl group such as triethylsilyl. A person skilled in the art will also appreciate other orthogonal protection strategies, available by conventional means as described in Theodora W Greene (see above).

15

The deprotection to yield a compound of formula (I), (Ia) or (Ib) may be effected using conventional techniques. Thus, for example, when R⁸, and/or R⁹ is an aralkyl group, this may be cleaved by hydrogenolysis in the presence of a metal catalyst (e.g. palladium on charcoal and/or palladium hydroxide on carbon).

20

When R⁸ is tetrahydropyranyl this may be cleaved by hydrolysis under acidic conditions. Acyl groups represented by R⁹ may be removed by hydrolysis, for example with a base such as sodium hydroxide, or a group such as trichloroethoxycarbonyl may be removed by reduction with, for example, zinc and acetic acid. Other deprotection methods may be found in Theodora W Greene (see above).

25

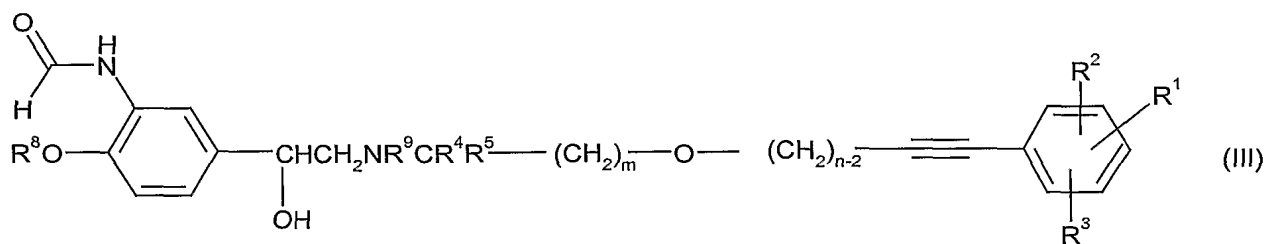
The enantiomeric compounds of the invention may be obtained (i) by separation of the components of the corresponding racemic mixture, for example, by means of a chiral chromatography column, enzymic resolution methods, or preparing and separating suitable diastereoisomers, or (ii) by direct synthesis from the appropriate chiral

30 intermediates by the methods described herein.

Optional conversions of a compound of formula (I), (Ia) or (Ib) to a corresponding salt may conveniently be effected by reaction with the appropriate acid or base. Optional

conversion of a compound of formula (I), (Ia) or (Ib) to a corresponding solvate or physiologically functional derivative may be effected by methods known to those skilled in the art.

- 5 Compounds of formulae (I) and (II) may be prepared from the corresponding compound of formula (III):



10

or a salt or solvate thereof, wherein R^1 , R^2 , R^3 , R^4 , R^5 , m , and n are as defined for the compound of formula (I) or (II), and R^8 , and R^9 are each independently hydrogen or a protecting group.

15

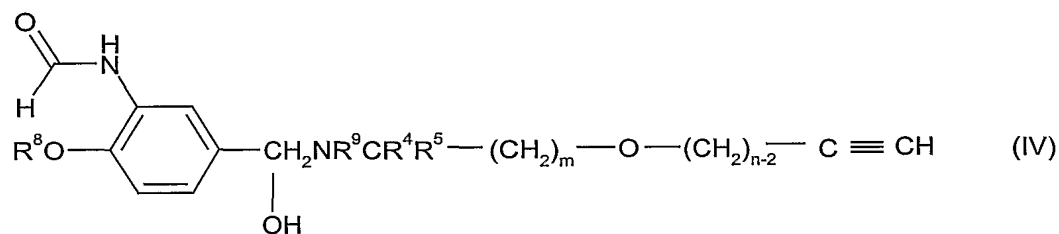
The conversion of a compound of formula (III) to a compound of formula (I) or (II) may be effected by reducing the triple bond. The reduction may be effected by any suitable method such as hydrogenation in the presence of a catalyst, for example, palladium/charcoal, palladium hydroxide on carbon, or platinum oxide.

20

If R^8 and/or R^9 is a protecting group which is cleavable by hydrogenolysis, then it may be removed under the conditions used for the reduction of the triple bond in the compound of formula (III) to give a compound of formula (I) directly or a compound of formula (II) wherein one of R^8 and R^9 is hydrogen.

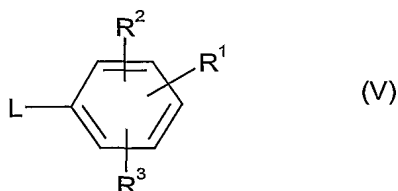
25

Compounds of formula (III) may be prepared from the corresponding compound of formula (IV):



or a salt or solvate thereof, wherein R^4 , R^5 , R^8 , R^9 , m and n are as defined for the compound of formula (III);

5 by coupling with a compound of formula (V):



10 wherein R^1 , R^2 , and R^3 are as defined for the compound of formula (III) and L is a leaving group, such as a halo group (typically, bromo or iodo) or a sulphonate ester such as a haloalkyl sulphonate (typically, trifluoromethanesulphonate), or a precursor thereof (wherein one or more of the substituents R^1 , R^2 or R^3 is a group which is convertible to the desired group R^1 , R^2 , or R^3).

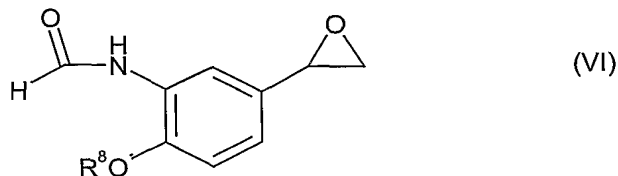
15 .

The coupling of compound of formula (IV) with a compound of formula (V) is conveniently effected in the presence of a catalyst system such as bis (triphenylphosphine) palladium dichloride with cuprous iodide and an organic base such as a trialkylamine, for example, triethylamine, in a suitable solvent, for example
20 acetonitrile or dimethylformamide.

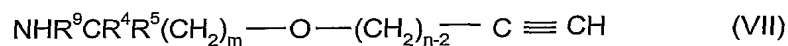
Compounds of formula (V) are commercially available or may be prepared by methods well known to the person skilled in the art.

25 Compounds of formula (IV) may be prepared by coupling a compound of formula (VI):

25



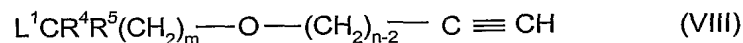
or a salt or solvate thereof, wherein R^8 is as defined for the compound of formula (IV),
 5 with a compound of formula (VII):



wherein R^4 , R^5 , R^9 , m and n are as defined for the compound of formula (II).

The coupling of a compound of formula (VI) with a compound of formula (VII) may be
 effected by simply mixing and optionally heating the compounds together, either neat or
 in a solvent, for example an aprotic solvent such as dimethylformamide or an alcohol
 such as n-butanol.

Compounds of formula (VII) may be prepared by coupling a compound of formula (VIII):



wherein R^4 , R^5 , m and n are as defined for the compound of formula (I)
 and L^1 is a leaving group, for example a halo group (typically bromo or iodo) or a
 sulphonate such as an alkyl sulphonate (typically, methanesulphonate), an
 arylsulphonate (typically, toluenesulphonate), or a haloalkyl sulphonate (typically,
 trifluoromethanesulphonate),

with a compound of formula (IX):



wherein R⁹ is as defined for the compound of formula (III).

5 The coupling of a compound of formula (VIII) with a compound of formula (IX) may be effected by simply mixing and optionally heating the compounds together, either neat or in an aprotic solvent, for example dimethylformamide.

10 Compounds of formula (VIII) may be prepared from the corresponding dihaloalkane and hydroxyalkyne by conventional chemistry, typically in the presence of an inorganic base, such as aqueous sodium hydroxide, under phase transfer conditions in the presence of a salt such as tetraalkylammonium bromide.

15 The compounds of formula (IX) are commercially available or may be prepared by methods well known to the person skilled in the art.

The compounds of formula (VI) are known in the art, for example in ES-A2005492 and R. Hett et al, Organic Process Research and Development, 1998, 2, 96-99, or may be prepared by methods well known to the person skilled in the art.

20 For a better understanding of the invention, the following Examples are given by way of illustration.

SYNTHETIC EXAMPLES

25 Throughout the examples, the following abbreviations are used:

LCMS: Liquid Chromatography Mass Spectrometry.

RT : retention time

THF : tetrahydrofuran

DMF : N,N-dimethylformamide

30 bp : boiling point

ca : circa

h : hour(s)

min : minute(s)

All temperatures are given in degrees centigrade.

Silica gel refers to Merck silica gel 60 Art number 7734.

Flash silica gel refers to Merck silica gel 60 Art number 9385.

Biotage refers to prepacked silica gel cartridges containing KP-Sil run on flash 12i chromatography module.

Bond Elut are prepacked cartridges used in parallel purifications, normally under vacuum. These are commercially available from Varian.

LCMS was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID) eluting with 0.1% HCO₂H and 0.01 M ammonium acetate in water (solvent A), and 0.05% HCO₂H 5% water in acetonitrile (solvent B), using the following elution gradient 0-0.7 min 0%B, 0.7-4.2 min 100%B, 4.2-5.3 min 0%B, 5.3-5.5 min 0%B at a flow rate of 3 ml/min. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive and negative mode (ES+ve and ES-ve).

Example 1

3-(4-{[6-({(2R)-2-[3-(Formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}butyl)benzenesulfonamide compound with (2E)-but-2-enedioic acid (2:1)

i) 6-bromohexyl but-3-ynyl ether

3-Butyn-1-ol (42.4ml) was stirred vigorously with 1,6-dibromohexane (260ml) and tetrabutylammonium bisulphate (2.4g) in 50% aqueous sodium hydroxide solution (200ml) under nitrogen for 3 days. Water (ca 700ml) was added and the organic layer was separated. The aqueous layer was extracted twice with dichloromethane (2 x 100ml) and the combined organic layers were washed with water, dried (MgSO₄) and concentrated. The residue in petroleum ether (bp 40 - 60°) was loaded onto a column of silica gel (1.5kg) and the column was eluted with petroleum ether (bp 40 - 60°), then 10% diethyl ether in petroleum ether (bp 40 - 60°) to give the *title compound* (103.3g), δ (CDCl₃) 3.56(2H, t, J 7Hz), 3.47(2H, t, J 7Hz), 3.42(2H, t, J 7Hz), 2.45(2H, m), 1.99(1H, t, J 2Hz), 1.87(2H, m), 1.60(2H, m) and 1.50 to 1.33 (4H, m).

ii) N-Benzyl-6-(but-3-ynyloxy)hexan-1-amine

A mixture of 6-bromohexyl but-3-ynyl ether (21.5g) and benzylamine (49.3g) was heated at 120° for 2h. The mixture was cooled and partitioned between 2M hydrochloric acid (40ml) and ethyl acetate (2 x 200ml). The combined extracts were washed with an aqueous sodium bicarbonate solution (100ml), water (200ml) and dried (Na₂SO₄). The solvent was removed in vacuo and the residue was purified by chromatography (Merck 9385) eluting with 2% methanol/chloroform. The appropriate fractions were evaporated to give the *title compound* (25.3g). LCMS RT=2.2min.

iii) 5-((1R)-2-{Benzyl[6-(but-3-ynyloxy)hexyl]amino}-1-hydroxyethyl)-2-(benzyloxy)phenylformamide

A stirred mixture of 2-(benzyloxy -5 -[(2R)-oxiran-2-yl]phenylformamide (R Hett et al, Organic Process Research & Development, 1998, 2, 96-99) (8.6 g) and N-benzyl-6-(but-3-ynyloxy)hexan-1-amine (9.1 g) was heated at 120° for 2h. The mixture was purified by chromatography (Merck 9385) eluting with cyclohexane/ethyl acetate (2 :1) to give the *title compound* (13.47g). LCMS RT=2.68min.

iv) 3-(4-{[6-(Benzyl{(2R)-2-[4-(benzyloxy)-3-(formylamino)phenyl]-2-hydroxyethyl}amino)hexyl]oxy}but-1-ynyl)benzenesulfonamide

A stirred solution of 5-((1R)-2-{benzyl[6-(but-3-ynyloxy)hexyl]amino}-1-hydroxyethyl)-2-(benzyloxy)phenylformamide (500mg) and 3-iodobenzenesulfonamide (340mg) in acetonitrile (10ml) and triethylamine (10ml) with cuprous iodide (50mg) and bis(triphenylphosphine) palladium dichloride (100mg) was stirred at ambient temperature under nitrogen for 2h. The mixture was evaporated in vacuo and the residue was purified by chromatography on Biotage (40g) cartridge eluting with light petroleum 40-60° / ethyl acetate (9:1) to give the *title compound* (330 mg). LCMS RT=3.04min.

v) 3-(4-{[6-((2R)-2-[3-(Formylamino)-4-hydroxyphenyl]-2-hydroxyethyl)amino)hexyl]oxy}butyl)benzenesulfonamide compound with (2E)-but-2-enedioic acid (2:1)

A solution of 3-(4-{[6-(benzyl{(2R)-2-[4-(benzyloxy)-3-(formylamino)phenyl]-2-hydroxyethyl}amino)hexyl]oxy}but-1-ynyl)benzenesulfonamide (320mg) in ethanol

(15ml) was hydrogenated in the presence of 10% palladium on carbon (50mg) and palladium hydroxide on carbon (100mg) at 100p.s.i for 18h. The catalyst was filtered off onto celite and the filtrate was evaporated to dryness. The residual oil was purified by chromatography on Biotage (8g) cartridge eluting with dichloromethane/ethanol/0.88 ammonia (25:8:1). The residual oil (118mg) was dissolved in methanol (20ml) and treated with fumaric acid (0.5 equivalent) and evaporated to give the *title compound* (80mg). LCMS RT=2.39min, ES+ve 508 (MH)⁺.

Example 2

N-(tert-Butyl)-3-(4-{[6-({(2R)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}butyl)benzenesulfonamide

i) N-(tert-Butyl)-3-iodobenzenesulfonamide

tert-Butylamine (300mg) was added to a stirred, cooled (ice-bath) solution of 3-iodobenzenesulfonyl chloride (Bromidge et al, J. Med. Chem., 1999, 42(2), 202-205) and triethylamine (420mg) in dichloromethane (7ml). The mixture was then stirred for 2h at room temperature, diluted with dichloromethane (10ml) and washed with 2M hydrochloric acid (5ml). The mixture was separated on a hydrophobic frit and the organic phase was evaporated to give the *title compound* (1.26g). LCMS ES+ve 340 (MH)⁺

(ii) 3-(4-{[6-(Benzyl{(2R)-2-[4-(benzyloxy)-3-(formylamino)phenyl]-2-hydroxyethyl}amino)hexyl]oxy}but-1-ynyl)-N-(tert-butyl)benzenesulfonamide

was prepared by methods similar to those described in Example 1iv. TLC SiO₂, cyclohexane/ethyl acetate 1:1 R_f=0.37.

(iii) N-(tert-Butyl)-3-(4-{[6-({(2R)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}butyl)benzenesulfonamide

was prepared by methods similar to those described in Example 1v. LCMS RT=2.51 min, ES+ve 564 (MH)⁺

BIOLOGICAL ACTIVITY

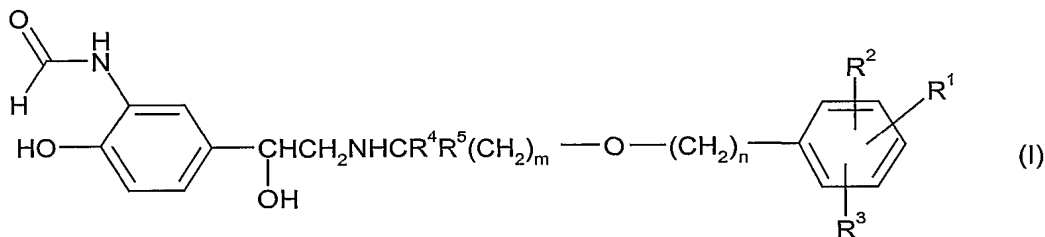
The potencies of the aforementioned compounds were determined using frog melanophores transfected with the human beta 2 adrenoreceptor. The cells were incubated with melatonin to induce pigment aggregation. Pigment dispersal was induced by compounds acting on the human beta 2 adrenoreceptor. The beta 2 agonist activity of test compounds was assessed by their ability to induce a change in light transmittance across a melanophore monolayer (a consequence of pigment dispersal). At the human beta 2 adrenoreceptor, compounds of examples 1 and 2 had IC₅₀ values below 1 μM.

Potency at other beta adrenoreceptor subtypes was determined using chinese hamster ovary cells transfected with either the human beta 1 adrenoreceptor or the human beta 3 adrenoreceptor. Agonist activity was assessed by measuring changes in intracellular cyclic AMP.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

Claims

1. A compound of formula (I)



or a salt, solvate, or physiologically functional derivative thereof, wherein:

m is an integer of from 2 to 8;

n is an integer of from 3 to 11;

with the proviso that m + n is 5 to 19;

R¹ is -XSO₂NR⁶R⁷

wherein X is -(CH₂)_p- or C₂₋₆ alkenylene;

R⁶ and R⁷ are independently selected from hydrogen, C₁₋₆alkyl,

C₃₋₇cycloalkyl, C(O)NR⁸R⁹, phenyl, and phenyl (C₁₋₄alkyl)-,

or R⁶ and R⁷, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7-membered nitrogen containing ring,

and R⁶ and R⁷ are each optionally substituted by one or two groups selected from halo, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, hydroxy-substituted C₁₋₆alkoxy, -CO₂R⁸, -SO₂NR⁸R⁹, -CONR⁸R⁹, -NR⁸C(O)R⁹, or a 5-, 6- or 7-membered heterocyclic ring;

R⁸ and R⁹ are independently selected from hydrogen, C₁₋₆alkyl,

C₃₋₆cycloalkyl, phenyl, and phenyl (C₁₋₄alkyl)-; and

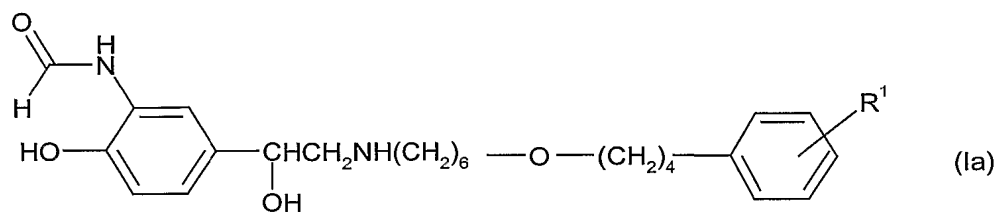
p is an integer of from 0 to 6;

R² and R³ are independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, halo, phenyl, and C₁₋₆haloalkyl;

R^4 and R^5 are independently selected from hydrogen and C_{1-4} alkyl with the proviso that the total number of carbon atoms in R^4 and R^5 is not more than 4.

2. A compound of formula (Ia)

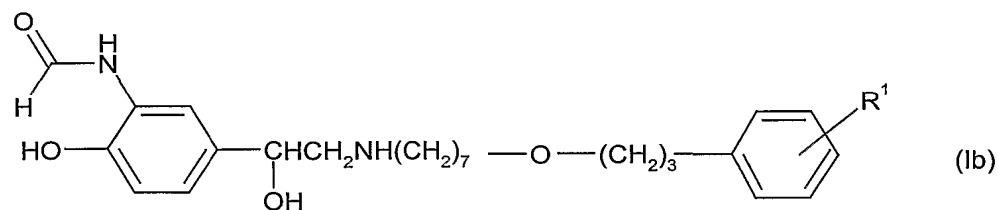
5



or a salt, solvate, or physiologically functional derivative thereof, wherein

- 10 R^1 is as defined in claim 1 for formula (I).

3. A compound of formula (Ib)



15

or a salt, solvate, or physiologically functional derivative thereof, wherein

R^1 is as defined in claim 1 for formula (I).

- 20 4. A compound of formula (I) or formula (Ia) selected from:
 3-(4-([6-((2R)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl)amino)hexyl]oxy)butyl)benzenesulfonamide;
 3-(4-([6-((2S)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl)amino)hexyl]oxy)butyl)benzenesulfonamide;

3-(4-{{6-({(2R/S)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl}oxy}butyl)benzenesulfonamide;
N-(tert-butyl)-3-(4-{{6-({(2R)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl}oxy}butyl)benzenesulfonamide;
5 N-(tert-butyl)-3-(4-{{6-({(2S)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl}oxy}butyl)benzenesulfonamide; and
N-(tert-butyl)-3-(4-{{6-({(2R/S)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl}oxy}butyl)benzenesulfonamide;
or a salt, solvate, or physiologically functional derivative thereof.

10

5. A method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of
15 formula (I), (Ia) or (Ib) according to any of claims 1 to 4, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

6. A compound of formula (I), (Ia) or (Ib) according to any of claims 1 to 4, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative
20 thereof for use in medical therapy.

7. A pharmaceutical formulation comprising a compound of formula (I), (Ia) or (Ib) according to any of claims 1 to 4, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable
25 carrier or excipient, and optionally one or more other therapeutic ingredients.

8. A combination comprising a compound of formula (I), (Ia) or (Ib) according to any of claims 1 to 4, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and one or more other therapeutic ingredients.

30

9. A combination according to claim 8 wherein the other therapeutic ingredient is a PDE4 inhibitor, a corticosteroid or an anticholinergic.

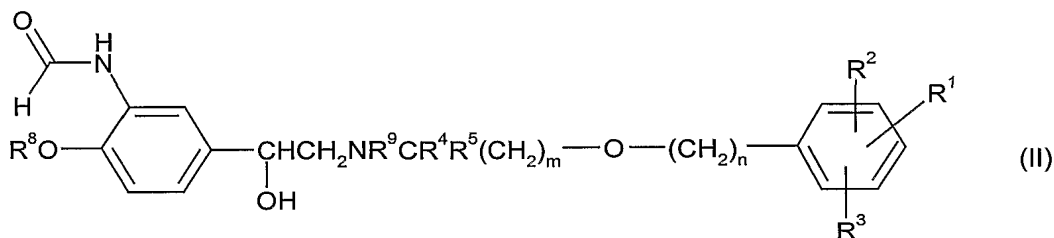
10. The use of a compound of formula according to any of claims 1 to 4, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2 -adrenoreceptor agonist is indicated.

5

11. A process for the preparation of a compound of formula (I), (Ia) or (Ib) according to any of claims 1 to 4, or a salt, solvate, or physiologically functional derivative thereof, which comprises:

(a) deprotection of a protected intermediate, for example of formula (II):

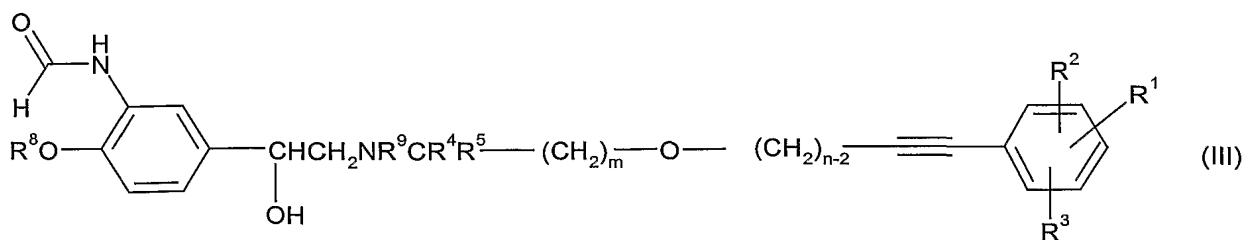
10



or a salt or solvate thereof, wherein R^1 , R^2 , R^3 , R^4 , R^5 , m , and n are as defined for the compound of formula (I) in claim 1, and R^8 , and R^9 , are each independently either hydrogen or a protecting group provided that at least one of R^8 , or R^9 , is a protecting group; or

15

(b) reduction of a compound of formula (III):



20

wherein R^1 , R^2 , R^3 , R^4 , R^5 , m , and n are as defined for the compound of formula (I) in claim 1, and R^8 , and R^9 , are each independently either hydrogen or a protecting group;

followed by the following steps in any order:

- (i) optional removal of any protecting groups;
- (ii) optional separation of an enantiomer from a mixture of enantiomers;
- 5 (iii) optional conversion of the product to a corresponding salt, solvate,
or physiologically functional derivative thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/03122

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C311/29 A61K31/18 A61P11/06 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	D. IAKOVIDIS, ET AL.: "Synthesis and beta-adrenoceptor agonist properties of (+/-)-1-(3',4'-dihydroxyphenoxy)-3-(3",4"-dimethoxyphenyl)ethylamino-2-propanol hydrochloride, (+/-)-R0363.HCl, and the (2S)-(-)-isomer" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 34, no. 6, June 1999 (1999-06), pages 539-548, XP004180361 Editions Scientifiques Elsevier, Paris, FR ISSN: 0223-5234 table I	1-10
A	US 5 066 678 A (H. FINCH, ET AL.) 19 November 1991 (1991-11-19) column 1 -column 2; example 8 --- -/--	1-10

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

8 August 2002

Date of mailing of the international search report

16/08/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

English, R

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/03122

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 140 800 A (GLAXO) 5 December 1984 (1984-12-05) cited in the application the whole document -----	1-10

INTERNATIONAL SEARCH REPORT

international application No.
PCT/EP 02/03122

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 5 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/03122

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5066678	A	19-11-1991	AT 100438 T	15-02-1994
			AU 631865 B2	10-12-1992
			AU 5377790 A	25-10-1990
			CA 2015188 A1	24-10-1990
			DE 69006107 D1	03-03-1994
			DE 69006107 T2	05-05-1994
			EP 0401966 A1	12-12-1990
			JP 3072448 A	27-03-1991
			NZ 233414 A	25-09-1992
			PT 93844 A	20-11-1990
			ZA 9003049 A	29-05-1991
GB 2140800	A	05-12-1984	AT 390611 B	11-06-1990
			AT 129184 A	15-11-1989
			AU 573212 B2	02-06-1988
			AU 2706484 A	25-10-1984
			BE 899448 A1	18-10-1984
			BE 900835 A4	17-04-1985
			BG 61490 B2	30-09-1997
			CA 1335999 A1	20-06-1995
			CA 1336004 A1	20-06-1995
			CH 661497 A5	31-07-1987
			CH 667084 A5	15-09-1988
			CZ 9104028 A3	12-05-1993
			CY 1482 A	08-12-1989
			CZ 285602 B6	15-09-1999
			DE 3414752 A1	18-10-1984
			DE 3448338 C2	19-05-1993
			DE 3448452 C2	05-01-1994
			DK 158092 A	30-12-1992
			DK 201784 A	19-10-1984
			ES 531722 D0	01-06-1985
			ES 8505641 A1	01-10-1985
			ES 539625 D0	16-07-1986
			ES 8609209 A1	16-12-1986
			FI 841548 A ,B,	19-10-1984
			FR 2545482 A1	09-11-1984
			GB 2176476 A ,B	31-12-1986
			GR 79925 A1	31-10-1984
			HK 36889 A	12-05-1989
			HU 200160 B	28-04-1990
			IE 57237 B1	17-06-1992
			IL 71569 A	30-10-1987
			IT 1199112 B	30-12-1988
			JP 1862136 C	08-08-1994
			JP 5069817 B	01-10-1993
			JP 63264443 A	01-11-1988
			JP 1643826 C	28-02-1992
			JP 3000858 B	09-01-1991
			JP 59199659 A	12-11-1984
			JP 2001385 C	20-12-1995
			JP 6087800 A	29-03-1994
			JP 7029997 B	05-04-1995
			KE 3864 A	19-05-1989
			KR 9204186 B1	30-05-1992
			LU 85329 A1	04-06-1985
			LU 88265 A9	03-02-1994
			MX 9203226 A1	01-07-1992

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/03122

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2140800	A	NL 8401258 A ,B,	16-11-1984
		NO 841568 A ,B,	19-10-1984
		NZ 207885 A	29-11-1988
		NZ 221999 A	29-11-1988
<hr/>			